

Notice of Allowability

Application No.

09/211,691

Applicant(s)

GILBERT ET AL.

Examiner

Art Unit

Manjunath N. Rao, Ph.D.

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the paper filed on 11-27-06.
2. ☒ The allowed claim(s) is/are 37-40 and 44-51.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
- (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
- 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
- (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892) | 5. <input type="checkbox"/> Notice of Informal Patent Application |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 6. <input type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date _____. |
| 3. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 8. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| | 9. <input type="checkbox"/> Other _____. |

DETAILED ACTION

Claims 37-40, 44-51 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 11-27-06, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Ms. Beth Kelly on 2-15-07.

The application has been amended as follows:

In the claims:

- A) In claim 46, line 3, delete "claim 45" and replace with "claim 44".
- B) In claim 46, line 5, delete the first recitation of "the" and replace with "said".
- C) In claim 49, line 3, delete the first and the second recitation of the word "of".

Allowable Subject Matter

Claims 37-40, 44-51 are allowed.

The following is an examiner's statement of reasons for allowance: Following a diligent search it was determined that the prior art neither teaches nor suggests an isolated nucleic acid that encodes a fusion polypeptide wherein the fusion polypeptide comprises the two polypeptides as claimed in claims 37-40, 44-51. Examiner has withdrawn the previous rejections in view of the claim amendments filed on 11-27-06. Examiner has also allowed the instant claims based on the contents of the Declaration provided by Dr. Paulson who has filed said affidavit as an expert in the field. Dr. Paulson, in his Declaration has clearly explained that when the instant application was filed in 1997, questions had been raised about the validity of proximity effect disclosed in Bulow et al. which relies on diffusion or Brownian motion for transport of a reaction intermediate between two active sites on a bi-functional fusion protein. Dr. Paulson explains that researchers demonstrated that Brownian motion was not sufficient to transfer a coupled reaction intermediate from the active site of one protein to the active site of its fusion partner and that researchers then proposed that the arrangement of charged residues on a fusion protein allowed electrostatic surface diffusion or channeled transfer of an intermediate from the active site of one protein to the active site of its fusion partner and that this channeled transfer or substrate channeling was believed to enhance reaction kinetics and explain the so-called proximity effect. The Declaration also explains that researchers were not able to reproduce even that kind of substrate channeling in a synthetic bi-functional fusion protein, even though the structure of a naturally occurring bi-functional fusion protein, the Leishmania dihydrofolate reductase-thymidylate synthase (DHFR-TS) expressed in *E. coli* as two separate mono-

Art Unit: 1652

functional enzymes was available as a model. The Declaration explains that the synthetic *E. coli* DHFR-TS bi-functional fusion protein did not exhibit substrate channeling and that Trujillo et al. concluded that "the local concentration of H₂-folate obtained by linking the mono-functional *E. coli* enzymes is not sufficient to promote substrate channeling" thereby demonstrating that substrate channeling, i.e., a proximity effect, did not occur in the synthetic *E. coli* DHFR-TS fusion protein. The Declaration also concludes that any "advantage" resulting from alleged proximity effects is not conserved during evolution i.e., it cannot be expected of any or all fusion proteins. The Declaration further goes on to state that the proximity effect could not reliably be generated in synthetic fusion proteins, and the proposed advantage of a bi-functional fusion protein over mono-functional proteins was doubted and that papers that build on the results of Trujillo et al. and discredit the proximity effect continue to be published. The Declaration finally states that a co-author of Bulow et al. paper has now concluded that "bringing two sequential enzymes together in a fusion protein..., is obviously not sufficient to cause any kinetically significant metabolite channeling through proximity effects." It is only the fusion protein comprising the α 2,3-sialyltransferase and the CMP-Neu5Ac synthetase of *N.meningitidis* which applicants claim herein that functions as a bi-functional enzyme. Therefore based on the Declaration of Dr. Paulson et al. Examiner takes the position that not any or all enzymes can be simply made as a functional fusion protein with bi-functional activities and that is possible to do so only with specific polynucleotides of *N.meningitidis* as claimed herein.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

Art Unit: 1652

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

February 19, 2007